Online Supplement

Limit of Detection of Troponin discharge strategy versus usual care: a randomised controlled trial

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Carlton EW, *et al. Heart* 2020; 106:1586–1594. doi: 10.1136/heartjnl-2020-316692

Detailed Methodology

Clinical Management and Data Collection

The decision to discharge a patient was made after clinical assessment and once hs-cTn results were available (for either intervention or control strategies). This decision was made entirely at the discretion of the treating clinician. Where there was ongoing clinical concern (in the absence of abnormal hs-cTn results) patients were admitted accordingly and reasons for deviation from the recommended strategy recorded. Given this was a trial embedded within routine ED practice, where clinical assessment was delayed (for example beyond four hours after arrival), patient data were included in an intention to diagnose analysis. Onward referral for outpatient investigation, for example to a "chest pain clinic", followed local guidance and was not altered for trial purposes.

We collected clinical information on a bespoke case report form for each patient including: demographic data; symptom onset time; symptomatology; risk factors for coronary artery disease; past medical history; hs-cTn results; discharge time; discharge destination. Patient arrival and discharge times were extracted from ED electronic information systems, or in the case of admitted patients, from inpatient discharge summaries.

Follow-up processes

All patients who had their clinical care potentially altered through trial enrolment, i.e. those with an initial undetectable hs-cTn, were followed-up 30 days after the index ED attendance by telephone call. Patient reported data were collected to capture information about any adverse events and or other health service use since discharge. Where potential adverse events were identified from patient reporting, these were corroborated or clarified from hospital or primary care records. Patients with an initial detectable hs-cTn, were followed up through a screening text message confirming the absence of subsequent events. Where events were reported or patients failed to respond, hospital and primary care records were again interrogated.

Secondary outcomes were: 1) median length of hospital stay (ED/ED Observation Unit/admitted); 2) incidence of MACE occurring within 30 days of ED attendance; 3) adherence to the LoDED strategy; 4) comparative costs; 5) acceptability of the intervention (from patient satisfaction and an embedded qualitative study). An additional outcome analysis of successful early discharge (within four hours of ED arrival and without 30-day

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MACE) in patients with an initial undetectable hs-cTn was agreed by the trial steering committee prior to unmasking.

Detailed methodology for both the health economic analysis and the qualitative study are available in a published study protocol.[1] Briefly, for the cost comparison we valued secondary care resource use over 30 days from the perspective of the UK NHS. For the embedded qualitative study semi-structured telephone interviews were conducted with a purposive sample of intervention participants from four sites after their 30-day follow-up contact. In addition, two focus groups with ED doctors, nurses and general practitioners (GPs) were held at two sites.

Statistical and health economic analysis

The binary primary outcome was analysed by carrying out separate logistic regression by centre, adjusting for age and sex using all those randomised with complete data in an intention-to-diagnose analysis to produce adjusted odds ratios and 95% confidence intervals for each centre. As the usual care pathway differed between sites, it was anticipated *a priori* that the proportion of patients discharged within four hours in the control arm would vary, which could influence the treatment effect observed at each centre. In order to allow pooling of the odds ratios across sites to obtain an overall odds ratio, we used a meta-analysis methodology. The between centre heterogeneity was examined in the adjusted odds ratios using the Q and I^2 statistic to describe the percentage of variation across centres that was due to heterogeneity rather than chance. An overall pooled odds ratio was obtained by fitting centre as a random effect. As significant heterogeneity between centres was identified, the potential reasons were investigated further by completing separate post-hoc subgroup analyses; in sites with and without the undetectable cut-off in usual rule-out strategies and by hs-cTn assay type.

Kaplan Meier-type graphs were used to illustrate the relationship between length of hospital stay and allocated group. Descriptive statistics were also reported.

These analysis methods were repeated for the additional analysis for the subgroup of those with an initial undetectable hs-cTn, although small numbers of participants in some sites meant that it was not possible to adjust for age and sex in this logistic regression model.

The primary economic analysis valued the secondary care resource use of the intention-to-diagnose population over 30 days from the perspective of the UK NHS (intervention versus control). Additionally, a subgroup analysis considered the primary and community care (defined as subsequent ED, GP and outpatient contacts) in addition to the secondary care costs for those patients with an initial undetectable hs-cTn. To inform cost estimates national sources of unit costs were first attached to per-patient quantities of health resource for different health resource categories (Table S1). We then calculated total quantities of resource use, and mean per-patient costs for each resource category. We report the per-patient sum of these costs and their incremental differences with 95% CI, (age sex adjusted for the primary economic analysis).

Additional Reporting

Patients with an initial undetectable high-sensitivity cardiac troponin

Data on the initial hs-cTn result were available in 611/629 (97%) of patients. Of these, 274 (45%) had an initial undetectable hs-cTn. No patient presenting with an initial undetectable hs-cTn had a MACE at 30 days. The characteristics of patients with an initial undetectable hs-cTn are shown in Table S2. This subgroup had a lower mean age (45.4 years), and a higher proportion of females (53%), compared to the whole cohort.
More patients with an initial undetectable hs-cTn were successfully discharged within four hours of arrival when allocated to the LoDED strategy (97/137 [71%]) compared to usual rule-out strategies (68 of 132 [52%]) (Table 3: Main Manuscript). Again, significant heterogeneity was noted between centres (I^2 = 66%, p = 0.005 for Q test); pooled odds ratio of 2.51 (95% CI 0.76-8.25). For this subgroup the Kaplan Meier-type length of stay curve demonstrates clear separation between the control and intervention groups that persists until eight hours after presentation (Figure 3: Main Manuscript).

Comparative costs

Complete resource use data was available for 590 of the 629 patients. For the intention to diagnose economic analysis, mean secondary care costs across all sites were higher (by £98: 95%CI £-131 to £332) for the LoDED strategy compared to usual care, however this

difference was not statistically significant and was similar when adjustment for age and sex was applied (Table 3: Main Manuscript).

In the subgroup analysis, patients with an initial undetectable hs-cTn had slightly higher (by £29:95% CI £-33 to £99) total NHS costs compared to those receiving usual care (Table 3). There were no substantial differences at a patient level in post discharge primary/community and secondary care costs of the various resource categories between strategies in those patients with an initial undetectable hs-cTn (Table 4: Main Manuscript). Similar frequencies and costs of primary care contacts were observed in both strategies (107 contacts across 53% of patients in LoDED *vs.*105 contacts from 49% of patients for usual care) (Table 4). The frequency and proportion of patients having further cardiac testing was low overall, but higher with the LoDED strategy (15 tests across 11% of patients) compared with usual care (9 tests across 5% of patients). This accounted for only a small difference in costs (£13 compared to £6, Table 4). The cost of subsequent ED contacts was higher in the LoDED arm, but the difference can be explained by one patient attending the ED multiple times (Table 4: Main Manuscript).

Table S1 Resource categories and unit costs (Comparative Costs analysis)

Trail cost	Cost (£)	Source*
Initial Emergency Department (ED) attendance	*Source National Schedule of Reference Costs 2017/18 unless otherwise stated (1).	
Time in ED and ED observation ward	£15.08/ hour	**HRG Code** - EB12C Unspecified chest pain CC score 0-4 (Pro-rata) Method similar to that used in Goodacre et al., 2011(2)
High-sensitivity troponin test	£5.52	Direct from North Bristol Trust (NBT) plus staff costs for 5mins.
Electrocardiogram (ECG)	£9.57	ECG machine based on 1,000 uses, disposables, and Nurse time for 10mins (3) Inflated using PSSRU (4) 'health services (HCHS) index'
Hospital Stay		
Coronary care	£1,449 (No trim-point)	**HRG code** -Weighted average of XC01Z–XC07Z Adult critical care
Confirmed Myocardial infarction	£1,514 (+327)	**HRG Code** - Weighted average of EB10A-EB10E – Actual or Suspected MI CC score 0-13+ (Excess bed days cost added at length of stay over 8.5 days based on weighted average of trim points)
Medical admissions ward	£432 (+338)	**HRG Code** - Weighted average of EB12A-EB12C– Unspecified chest pain (Excess bed days cost added at length of stay over 3.15 days based on weighted average of trimpoints)
Subsequent hospital stay	£432 (+338)	**HRG Code** - Weighted average of EB12A-EB12C Assumed the same as admissions ward (Excess bed days cost added at length of stay over 3 days based on weighted average of trimpoints)
Hospital Treatments		
Cardiac Stent	£3,886	**HRG Code** - Weighted average YR12Z- YR15C Percutaneous Transluminal Angioplasty with Insertion of Stent Graft
Coronary Artery bypass	£10,709	**HRG Code** - Weighted average ED26A – ED28C Artery Bypass
Pacemaker	£3,326	**HRG Code**-Weighted average EY04A- EY08E Pacemaker
Other hospital tests		
Echocardiogram	£97	**HRG Code** - RD51A Simple Echocardiogram
Exercise stress test	£120	**HRG Code** - EC22Z – Electrocardiogram Monitoring or Stress Testing, for Congenital Heart Disease
Stress echocardiogram	£120	**HRG Code** - EC22Z Electrocardiogram Monitoring or Stress Testing, for Congenital Heart Disease
24hr heart monitor	£120	**HRG Code** - EC22Z – Electrocardiogram Monitoring or Stress Testing, for Congenital Heart Disease
Abdominal ultrasound	£55.37	**HRG Code** - Weighted average RD40Z - RD46Z Ultrasound Scan
CT coronary angiogram	£100.89	**HRG Code** - Weighted average RD20A - RD21A & RD22Z-RD27Z CT Scan
Coronary angiography	£151.01	**HRG Code** - Weighted average of RD30Z-RD35Z Contrast Fluoroscopy Procedures
Other Health Services		
Telephone health advice (e.g. 111)	£20 per interaction	**PSSRU**(4) – Average of GP telephone consultation (with qualification) and 111(5)
GP surgery practice – (9.2min contact)	£37.40 per consultation	**PSSRU**(4) Cost of GP consultation (direct care staff cost with qualifications)
Nurse (GP) - (9.7 min contact(6))	£6.79 per consultation	**PSSRU** (4) -Nurse (GP) Face-to-face consultation (with qualifications)
ED attendance	£160 per interaction	**HRG Code** - Weighted average VB01Z- VB09Z Emergency Medicine
Outpatient visit	£134 per appointment	**PSSRU**(4) – National weighted average of all outpatient attendances
Cardiac outpatient	£134 per appointment	**HRG code**- Service code 320 Cardiology outpatient visit

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Table S2. Demographics and risk characteristics for patients with an initial high-sensitivity cardiac troponin below the Limit of Detection

	Usual Care (n=133)	**LoDED Strategy (n=141)**	**All Patients (n=274)**
Age, mean (SD), y	45 (12)	46 (12)	45 (12)
Male sex, No. (%)	59 (44)	71 (50)	130 (48)
Ethnic Origin, No. (%)			
White	112 (85)	116 (82)	228 (84)
Chest Pain History (clinician reported) (%)			
Slightly Suspicious	86 (65)	89 (63)	175 (64)
Moderately Suspicious	39 (29)	38 (27)	77 (28)
Highly Suspicious	8 (6)	14 (10)	22 (8)
Prior History of Coronary Artery Disease (%)	6 (5)	6 (4)	12 (4)
Risk Factors for Coronary Artery Disease			
Hypercholesterolemia	10 (8)	12 (9)	22 (8)
Hypertension	13 (10)	23 (16)	36 (13)
Diabetes (treated)	3 (2)	9 (6)	12 (4)
Current smoking	27 (20)	30 (21)	57 (21)
Family History of Coronary Artery Disease (first degree relative under the age of 65 years)	31 (23)	28 (20)	59 (22)
Time in hours from chest pain onset to arrival in ED (median(IQR))	2·25 (1·48 – 3·48)	2·12 (1·33 – 3·38)	2·17 (1·37 – 3·43)

Table S4. Group Health of America Satisfaction Survey Completed on Discharge.[2]

	1. Poor	2. Fair	3. Good	4. Very Good	5. Excellent
The urgency with which you were assessed					
The thoroughness of your assessment					
Explanations given to you about medical procedures & tests					
Attention given to what you have to say					
Advice you got about ways to avoid illness and stay healthy					
Friendliness & courtesy shown to you by hospital staff					
Personal interest in you & your medical problems					
Respect shown to you, and attention to your privacy					
Reassurance & support offered to you by hospital staff					
Amount of time the hospital staff gave you					
Overall, how satisfied are you by the service you received?					

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Figure S1-8 Kaplan Meier-type length of stay curves buy site

Figure S1. Royal United Hospital, Bath

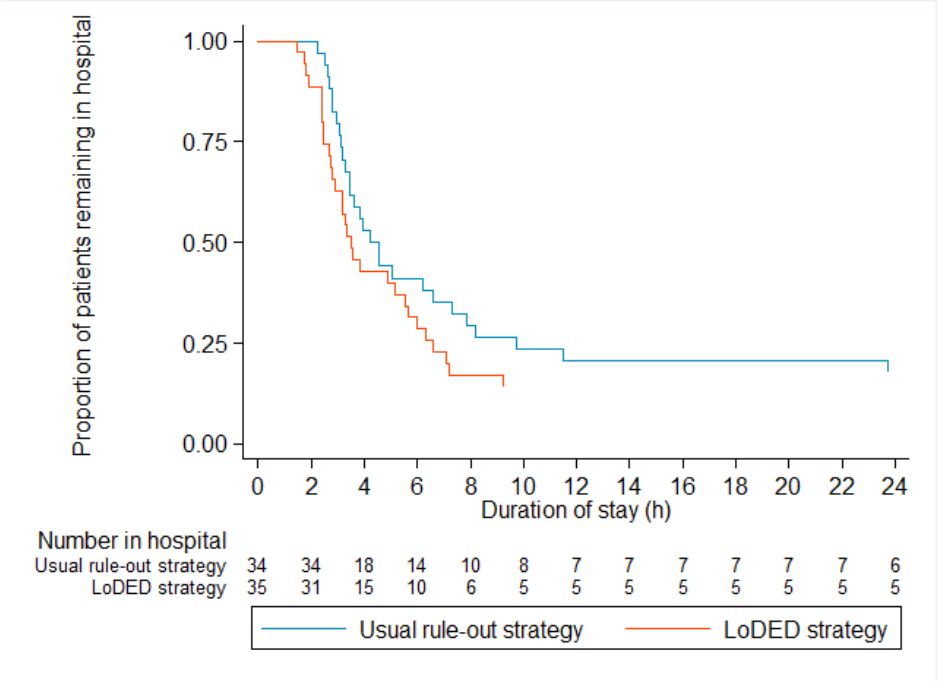


Figure S2. Southmead Hospital, Bristol

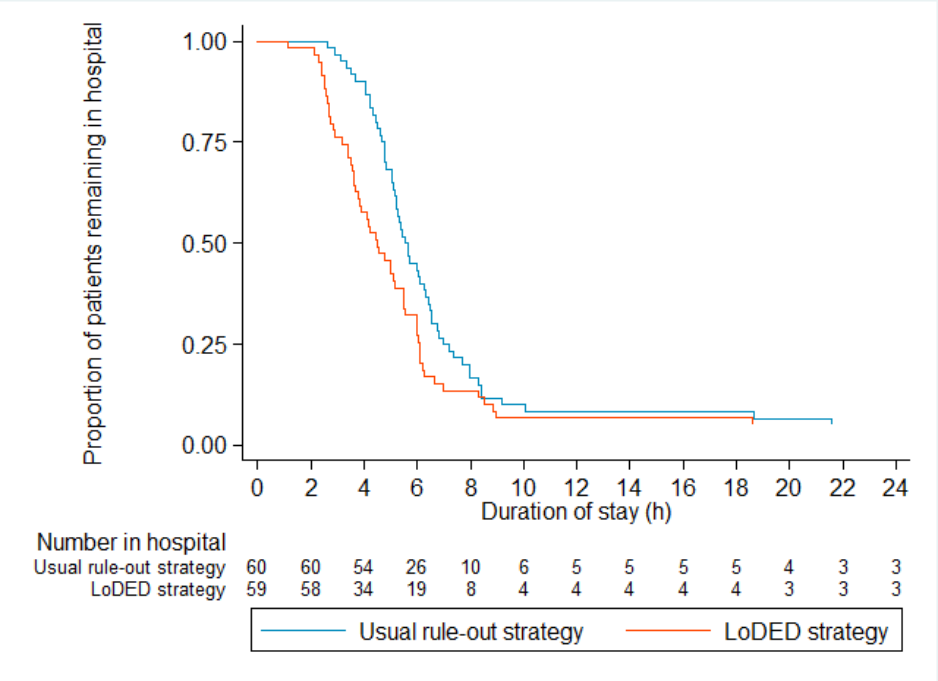


Figure S3. Derriford Hospital, Plymouth

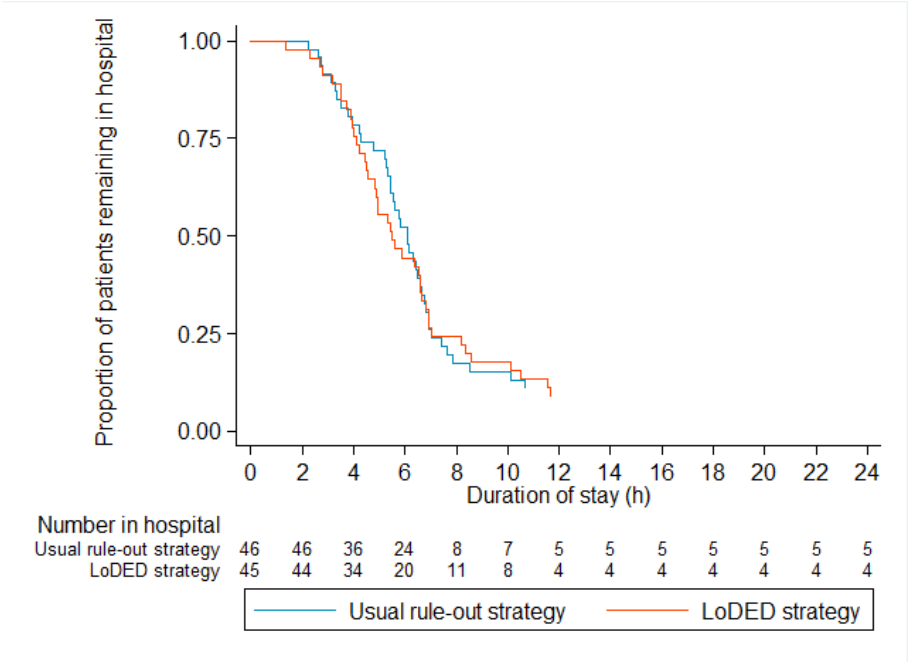


Figure S4. University Hospital, Southampton

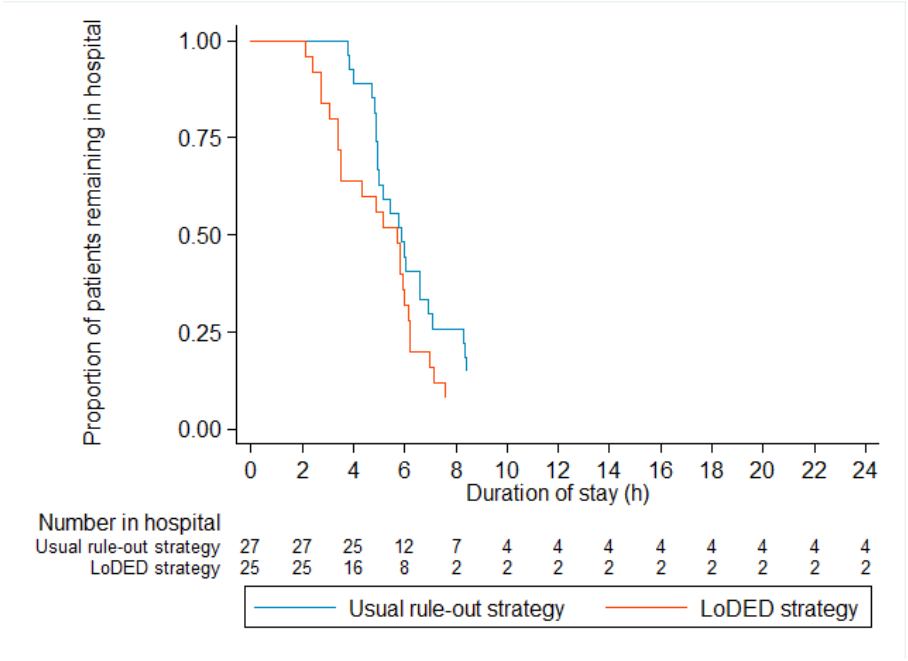


Figure S5. University Hospital of Wales, Cardiff

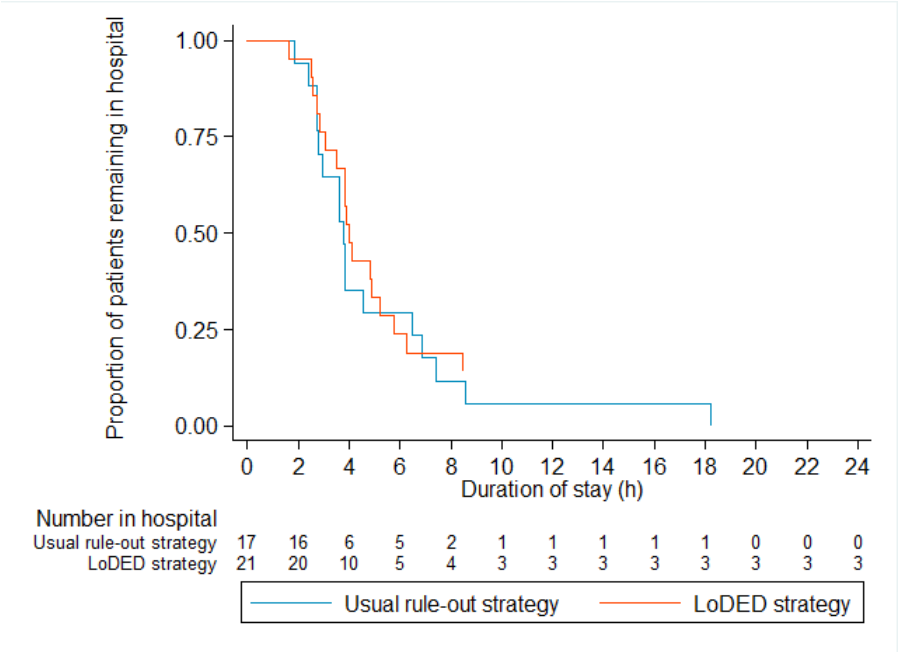


Figure S6. Royal Devon and Exeter Hospital, Exeter

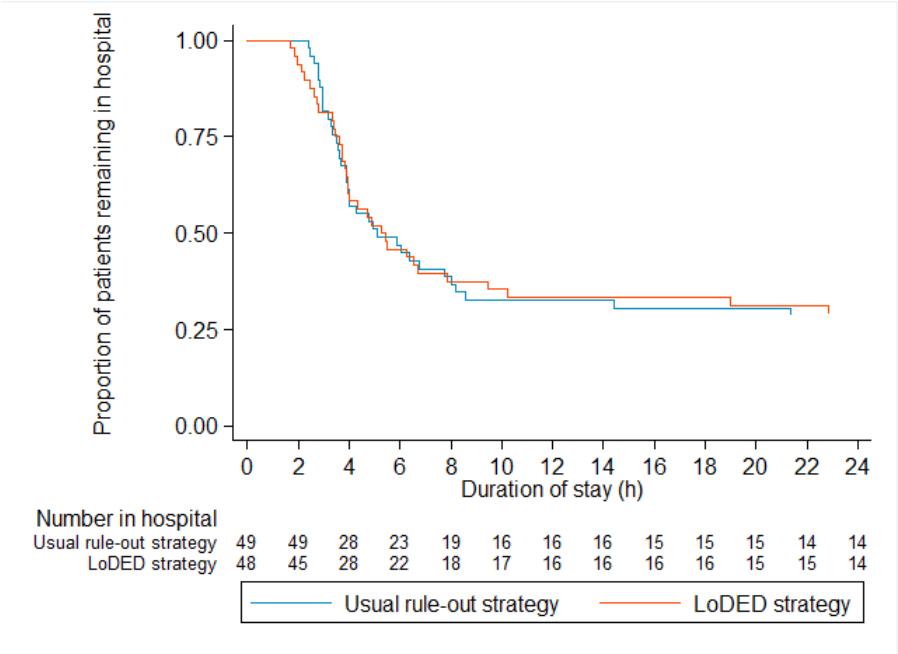


Figure S7. Royal London Hospital, Barts Health NHS Trust, London

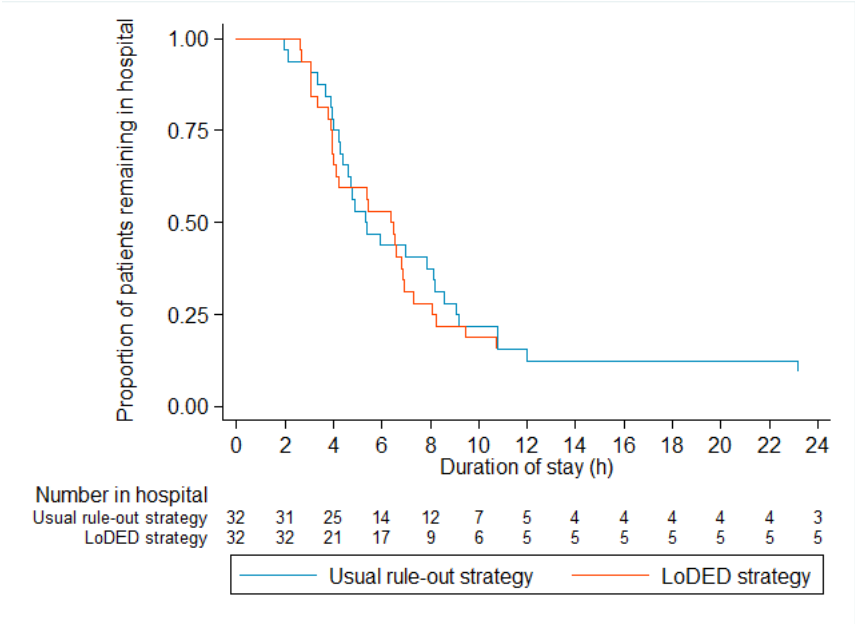
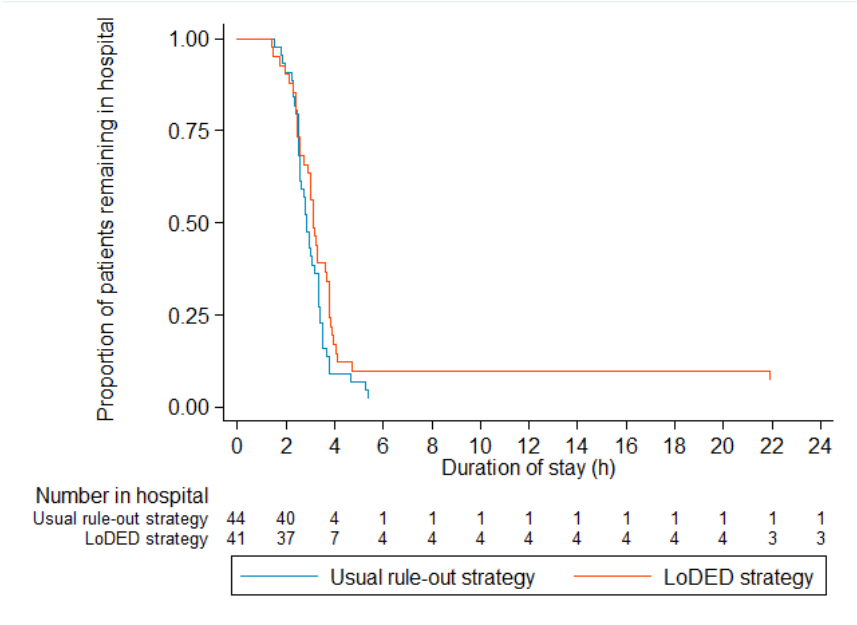


Figure S8. Royal Berkshire Hospital, Reading



References

1. Carlton E, Campbell S, Ingram J, et al. Randomised controlled trial of the Limit of Detection of Troponin and ECG Discharge (LoDED) strategy versus usual care in adult patients with chest pain attending the emergency department: study protocol. BMJ Open 2018;8:e025339.

2. NHS Improvement. National schedule of reference costs 2017/18, NHS Improvement.

3. S Goodacre MB, P Fitzgerald, E Cross, P Collinson, A Gray and AS Hall. The RATPAC (Randomised Assessment of Treatment using Panel Assay of Cardiac markers) trial: a randomised controlled trial of point-of-care cardiac markers in the emergency department. Health Technology Assessment 2011;15(23).

4. National Clinical Guidelines Centre. Preoperative Tests: Routine preoprative tests for elective surgery. 2015. Contract No.: Apendix M: Economic considerations for Delphi.

5. Curtis L, Burns A. Unit Costs of Health and Social Care 2018 Kent Academic Repository, University of Kent. 2018.

6. Pope C, Turnbull J, Jones J, Prichard J, Rowsell A, Halford S. Has the NHS 111 urgent care telephone service been a success? Case study and secondary data analysis in England. BMJ Open. 2017;7(5):e014815.

7. Stevens S, Bankhead C, Mukhtar T, et al. Patient-level and practice-level factors associated with consultation duration: a cross-sectional analysis of over one million consultations in English primary care. BMJ Open. 2017;7(11):e018261.